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Value of ABCG2 Q141K and Q126X genotyping in predicting risk of preeclampsia in Chinese Han women population

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ABSTRACT

Hyperuricemia (HUA) in women with preeclampsia (PE) not only indicates a reminder of severity but also contributes directly to the pathogenesis of PE. ATP-binding cassette subfamily G member 2 (*ABCG2*) has a very strong effect on the serum urate concentrations. Our aim was to investigate the association between polymorphisms of *ABCG2* with PE in Chinese Han female population. A cohort of 793 preeclamptic women (466 PE with HUA and 327 PE without HUA) and 744 normal pregnant women recruited in this study were genotyped for genetic distribution of Q141K (rs2231142) and Q126X (72552713) in *ABCG2* by the TaqMan allelic discrimination real-time PCR. There was no statistically significant difference of genotypic and allelic frequencies between PE and the normal pregnant women in Q141K ($X^2 = 1.11$, $P = 0.58$ by genotype; $X^2 = 0.32$, $P = 0.57$ by allele) and Q126X ($P = 0.33$ by genotype; $P = 0.33$ by allele), and no significant difference was found in the genetic distribution of Q141K and Q126X between PE with HUA, PE without HUA and controls. Additionally, this study observed no significant difference in genotypic and allelic distribution between early/late-onset PE with/without HUA or mild/severe PE with/without HUA and control subgroups. Based on our findings, the ABCG2 Q141K and Q126X polymorphisms may not be associated with PE in Chinese Han women.

1. Introduction

Preeclampsia (PE) is a serious and specific pregnancy multisystem complication characterized by new-onset hypertension and proteinuria after 20 weeks' gestation in a pregnant woman with previously normotensive pressure. As one of major maternal mortality and morbidity to woman and infants especially in economically poor regions, PE affects approximately 3–10% of nulliparous pregnant women, which appears particularly significant to screen and diagnose early for women at risk of PE [1]. Despite extensive researches have been made, the pathophysiologic mechanism of this disease remains obscure and needs to be elucidated.

Hyperuricemia (HUA), a metabolic disorder, has a high risk of monosodium urate crystal formation and is correlated with the severity of hypertension, renal dysfunction and endothelial dysfunction, which involve in the development of PE [2]. HUA is also complicated with nearly three quarters of PE women and the rise of HUA occurs as early as 10 weeks in PE women prior to the elevated blood pressure and the presence of proteinuria [3,4]. Moreover, the presence of HUA in the first trimester could increase 3.22 times risk of gestational hypertension and PE [5]. Furthermore, the presence of HUA in PE has increased risk of preterm birth, delivery of a small for gestational age fetal, morbidity and mortality [4,5]. Previous studies have indicated HUA may involve in the pathogenesis of abnormal placentation in the development of PE by inhibiting the endothelial function, inducing oxidative stress and stimulating the inflammatory response via activating the release of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6), free radicals and oxidized lipid [1,5]. Therefore, HUA is not only a common biochemical feature but also a contributor to the pathogenesis of PE. As uric acid (UA) comes from the metabolism of purine, the balance of production and excretion determines the serum level of UA [6]. UA is also affected by the heritability with excess of 30% and serum urate concentration is

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influenced by about 30 genetic loci by genome-wide association study (GWAS) such as *ABCG2* (ATP-binding cassette subfamily G member 2), *GLUT-9* (glucose transporter type 9), *URAT1* (urate anion transporter 1) and *PDZK1* (PDZ domain containing 1) [7–9].

ABCG2, also known as breast cancer resistance protein (*BCRP*), located on chromosome 4q22, encodes an ATP-binding cassette (ABC) transporter (2), a heretofore unknown 72-kDa membrane urate efflux transporter [10,11]. The production of ABC transporter is expressed on apical membrane of several tissues, such as kidney, intestine, liver and especially placenta tissue which remind us that the production of this gene may play a potential role in the placenta [12]. As a high-capacity urate transporter, ABCG2 mediates UA efflux and the concentration of ABCG2 expressed on the luminal membrane is significant in the serum urate secretion [10]. The common dysfunction of ABCG2 may increase serum urate levels by reducing the urate excretion of the kidneys and overloading the renal urate via reducing the urate excretion of the intestines [13]. The missense genetic variant (Q141K; rs2231142) and the nonsense variant (Q126X; rs72552713) in *ABCG2* are both functional SNPs that affect the nucleotide-binding domain of the ABCG2 protein [8,14]. The Q141K variant causes approximately 50% loss of the urate transporter function of ABCG2, while the Q126X SNP may lead to complete dysfunction of ABCG2 [15,16].

As the genetic factors involve in the progress of PE, we will explore the global association of the genetic variants of *ABCG2* and PE development. Therefore, independent researches on large-scale samples need to be conducted to indentify the possible relevance and the purpose of our study was to explore the genetic variants Q141K and Q126X in *ABCG2* and PE in Chinese Han women.

2. Materials and methods

2.1. Study populations

The populations in our study were recruited from a cohort of 793 preeclamptic women and 744 normal pregnant women of The Affiliated Hospital of Qingdao University, Yantaishan Hospital, Yantai Yuhuangding Hospital, Binzhou Medical University Hospital, Maternal and Child Health Care of Zaozhuang, Liaocheng People's Hospital and Linyi People's Hospital between January 2013 and June 2017. The preeclamptic women were divided into two groups, 466 PE with HUA and 327 PE without HUA. On the basis of the International Society for the Study of Hypertension in Pregnancy (ISSHP), the diagnostic criteria of PE was based on blood pressure of ≥140/90, as well as proteinuria of 24-hour urine protein of ≥300 mg/l or ≥1+ dipstick on two or more random specimens after 20 weeks of gestation [17]. For the diagnostic criteria of HUA in premenopausal women, the serum uric acid level(SUA) of the samples obtained at admission and delivery were both above 6.0 mg/dl on a normal purine diet [18,19]. The definition of severe PE was PE with one or more severe complications, including central nervous system, cardiorespiratory, haematological, renal, hepatic and feto-placental [20,21]. The mild PE was PE without any complications of the mentioned above. The division of early-onset PE and late-onset was PE diagnosed before and after 34 weeks of gestation [22].The age of PE and controls was matched (30.26 ± 5.00 and 30.56 ± 4.00 years old, $P = 0.203$). Both PE patients and controls have no previous history of gestational hypertension, metabolic syndrome, diabetes mellitus, hematological malignancies, rheumatologic diseases, blood transfusion and immunotherapy and so on. We excluded patients whose medication for HUA and hypertension related data were not available in the records and controls with history of HUA, heart diseases and kidney disorders from this study. This research was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University and all participants in this study signed the informed consent.

2.2. Genotyping

DNA was extracted from lymphocytes in peripheral blood with the Qiagen DNA extraction kit (Qiagen, Hilden, Germany). The polymorphisms of ABCG2 (Q141K, Q126X) were conducted by the TaqMan allelic discrimination real-time PCR. Applied Biosystems of Life Technologies (New York, USA) designed the Taqman probes and primers. The primers of Q141K were 5′-CACTCTGACGGTGAGAGAAAACTTA-3′ (forward) and 5′-AGTTCTCAGCAGCTCTTCGGCTTGC-3′ (reverse). The primers of Q126X were 5′-AATGCAAACCCACTAATACTTACTT-3′ (forward) and 5′-TACCACGTAACCTGAATTACATTTG-3′ (reverse). The polymerase chain reaction (PCR) was conducted in a 25 μL volume, containing of 1.25 μL 20 × SNP Genotyping Assay, 12.5 μL 2 × PCR Master Mix, and 50 ng DNA and 10.25 μL DNase-free water. The amplification procedure was conducted as follows: 95 °C for 3 min; 45 cycles of 95 °C for 15 s and 60 °C for 1 min. Each cycle the fluorescent signals of VIC/FAM-labeled probes were detected. C1000TM thermal cycler system and Bio-Rad CFX manager 3.0 software were performed to the analysis of genotype.

2.3. Statistical analysis

Statistical analysis was conducted by IBM SPSS Statistics 21.0 software (SPSS Inc, Chicago, IL, USA). We conducted the differences among the population-based case-control study by Student's *t*-test, one-way analysis of (ANOVA), LSD *t* test, Pearson's X^2test, and Hardy—Weinberg equilibrium (HWE). Demographic and clinical characteristic data were compared through ANOVA and LSD *t* test. The genetic distribution of the control was assessed by HWE. The differences of allelic and genotypic distributions between two groups were performed by Pearson's X^2test (Fisher's exact test was used when expected values were below 5). We used odds ratios (ORs) and 95% confidence intervals (CIs) to reveal the relative risk degree. $P < 0.05$ (two-tailed) was considered to be statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of PE with HUA, PE without HUA and normal pregnant women were displayed in Table 1. The maternal age of PE with HUA, PE without HUA and normal pregnant women was 29.80 ± 4.73, 31.02 ± 5.53 and

Table 1
Demographic and clinical characteristics of the PE with HUA, PE without HUA and normal pregnant women.

	PE with HUA	PE without HUA	Control
Maternal age (years)	(29.80 ± 4.73)*	31.02 ± 5.53	30.56 ± 4.00
UA (mg/dl)	(7.59 ± 1.25)*	(4.95 ± 0.96)*	(4.25 ± 0.89)*
Systolic blood pressure (mmHg)	161.42 ± 17.85	160.87 ± 20.34	(114.93 ± 10.37)*
Diastolic blood pressure (mmHg)	(105.81 ± 13.99)*	(103.63 ± 13.60)*	(73.46 ± 8.01)*
Birth weight (g)	(2303.22 ± 873.90)*	(2641.04 ± 927.03)*	(3363.09 ± 431.55)*
Gestational age at delivery (weeks)	35.20 ± 3.51	35.67 ± 5.58	(38.94 ± 3.85)*

Notes: * demonstrates the difference from the other two groups.

Table 2
Distribution of the genotypic and the allelic frequency of the ABCG2 Q141K and Q126X polymorphisms between PE, PE with HUA, PE without HUA and normal pregnant women.

			NO. of Controls	PE case				PE with HUA				PE without HUA			
			(744)	NO. (793)	X^2	*P*	OR (95% CI)	NO. (466)	X^2	*P*	OR (95% CI)	NO. (327)	X^2	*P*	OR (95% CI)
Q141K	Genotype frequencies	AA	54	69	1.11	0.58		47	3.07	0.22		22	0.47	0.79	
		AC	322	335				199				136			
		CC	368	389				220				169			
	Dominant	CC	368	389	0.03	0.87	1.02	220	0.58	0.45	1.09	169	0.45	0.50	0.92
		AA + AC	376	404			(0.83–1.24)	246			(0.87–1.38)	158			(0.71–1.19)
	Recessive	AA	54	69	1.09	0.30	0.82	47	3.00	0.08	0.70	22	0.10	0.76	1.09
		AC + CC	690	724			(0.57–1.12)	419			(0.46–1.05)	305			(0.65–1.81)
	Allele frequencies	A	430	473	0.32	0.57	0.96	293	1.77	0.18	0.87	180	0.42	0.52	1.07
		C	1058	1113			(0.82–1.12)	639			(0.74–1.06)	474			(0.87–1.31)
Q126X	Genotype frequencies	CT	6	3		0.33		2		0.72		1		0.68	
		CC	738	790				464				326			
	Allele frequencies	T	6	3		0.33	2.14	2		0.72	1.88	1		0.68	2.64
		C	1482	1583			(0.53–8.56)	930			(0.38–9.35)	653			(0.32–22.00)

30.56 ± 4.00 years old, respectively. The UA level of PE with HUA, PE without HUA and normal pregnant women was 7.59 ± 1.25, 4.95 ± 0.96 and 4.25 ± 0.89 mg/dl, respectively. The mean blood pressure (both systolic blood pressure and diastolic blood pressure) of the PE patients was greatly increased than the normal control as expected ($P < 0.001$). The mean systolic blood pressure of the PE with HUA and without HUA was no difference ($P > 0.05$), while PE with HUA was higher diastolic blood pressure than without HUA ($P < 0.001$). PE patients had lower birth weight of offspring, and PE with HUA is more obvious than without HUA in this case ($P < 0.001$). The PE patients had a higher prevalence of preterm birth than the normal pregnant women ($P < 0.001$), while the difference of PE with HUA and without HUA was not significant ($P > 0.05$).

3.2. Genotypic and allelic analysis

The distribution of the genotypic and allelic frequencies of ABCG2 Q141K and Q126X were displayed in Table 2. The control's genotypes for two polymorphisms were in accordance with HWE (the control of Q141K and Q126X: $X^2 = 2.11$, $P = 0.15$; $X^2 = 0.01$, $P = 0.91$, respectively).

In Table 2, no significant difference was found in the genotypic and allelic distribution of ABCG2 Q141K polymorphism between PE and the normal pregnant women ($X^2 = 1.11$, $P = 0.58$ by genotype; $X^2 = 0.32$, $P = 0.57$, $OR = 0.96$, 95% *CI* 0.82–1.12 by allele), and there was also no significant difference in genotype frequencies between PE and controls for dominant and recessive models ($X^2 = 0.03$, $P = 0.87$, $OR = 1.02$, 95% *CI* 0.83–1.24 by dominant genotype; $X^2 = 1.09$, $P = 0.30$, $OR = 0.82$, 95% *CI* 0.57–1.12 by recessive genotype). In addition, no association was observed in the genotype including dominant and recessive model and allele frequencies of Q141K between PE with HUA, PE without HUA and controls (PE with HUA: $X^2 = 3.07$, $P = 0.22$ by genotype; $X^2 = 0.58$, $P = 0.45$, $OR = 1.09$, 95% *CI* 0.87–1.38 by dominant model; $X^2 = 3.00$, $P = 0.08$, $OR = 0.70$, 95% *CI* 0.46–1.05 by recessive model; $X^2 = 1.77$, $P = 0.18$, $OR = 0.87$, 95% *CI* 0.74–1.06 by allele; PE without HUA: $X^2 = 0.47$, $P = 0.79$ by genotype; $X^2 = 0.45$, $P = 0.50$, $OR = 0.92$, 95% *CI* 0.71–1.19 by dominant model; $X^2 = 0.10$, $P = 0.76$, $OR = 1.09$, 95% *CI* 0.65–1.81 by recessive model; $X^2 = 0.42$, $P = 0.52$, $OR = 1.07$, 95% *CI* 0.87–1.31 by allele). As for the Q126X, the TT genotype was not detected in this research and no statistical significant in the genotypic and allelic allocations was found between PE and the normal ($P = 0.33$ by genotype; $P = 0.33$, $OR = 2.14$, 95% *CI* 0.53–8.56 by allele), and the statistical results showed also no significant difference between PE with HUA, PE without HUA and the healthy women ($P = 0.72$ by genotype, $P = 0.72$, $OR = 1.88$, 95% *CI* 0.38–9.35 by allele; $P = 0.68$ by genotype, $P = 0.68$, $OR = 2.64$, 95% *CI* 0.32–22.00 by allele).

Furthermore, PE with HUA and PE without HUA groups were divided into mild/serve PE with HUA and mild/serve PE without HUA for both SNPs. In Table 3, the statistical data displayed no significant difference between mild/severe PE with HUA, mild/severe PE without HUA and controls in Q141K (mild PE with HUA: $X^2 = 4.18$, $P = 0.12$ by genotype; $X^2 = 0.96$, $P = 0.33$, $OR = 0.81$, 95% *CI* 0.54–1.23 by allele; serve PE with HUA: $X^2 = 1.92$, $P = 0.38$ by genotype; $X^2 = 1.39$, P = 0.24, $OR = 0.90$, 95% *CI* 0.74–1.08 by allele; mild PE without HUA: $X^2 = 0.52$, $P = 0.77$ by genotype; $X^2 = 0.25$, $P = 0.62$,

Table 3
Comparison of the genotypic and the allelic frequency of the ABCG2 Q141K and Q126X polymorphisms between the mild/severe PE with HUA, mild/severe PE without HUA and normal pregnant women.

			No. of Controls (744)	Mild PE case								Severe PE case							
				With HUA (54)				Without HUA (67)				With HUA (412)				Without HUA (260)			
				No.	X^2	*P*	OR (95% CI)	No.	X^2	*P*	OR (95% CI)	No.	X^2	*P*	OR (95% CI)	No.	X^2	*P*	OR (95% CI)
Q141K	Genotype	AA	54	8	4.18	0.12		5	0.52	0.77		39	1.92	0.38		17	0.29	0.86	
	frequencies	AC	322	20				26				179				110			
		CC	368	26				36				194				133			
	Allele	A	430	36	0.96	0.33	0.81	36	0.25	0.62	1.11	258	1.39	0.24	0.90	144	0.23	0.63	1.06
	frequencies	C	1058	72			(0.54–1.23)	98			(0.74–1.65)	568			(0.74–1.08)	374			(0.85–1.32)
Q126X	Genotype	CT	6	1		0.39		0		1		1		0.43		1		0.69	
	frequencies	CC	738	53				66				411				259			
	Allele	T	6	1		0.39	0.43	0		1		1		0.43	3.32	1		0.69	2.10
	frequencies	C	1482	107			(0.05–3.63)	132				821			(0.40–27.66)	519			(0.25–17.50)

Table 4
Comparison of the genotypic and the allelic frequency of the ABCG2 Q141K and Q126X polymorphisms between the early/late-onset PE with HUA, early/late-onset PE without HUA and normal pregnant women.

			No. of Controls (744)	Early-onset PE case						Late-onset PE case						
				With HUA (253)			Without HUA (159)			With HUA (213)			Without HUA (168)			
				No.	X^2	*P*	OR (95% CI)	No.	X^2	. *P*	OR (95% CI)	No	X^2	*P*	OR (95% CI)	No.	X^2	*P*	OR (95% CI)
Q141K	Genotype frequencies	AA	54	21	0.33	0.85		11	1.14	0.56		26	5.34	0.07		11	0.12	0.94	
		AC	322	110				62				89				74			
		CC	328	122				86				98				83			
	Allele frequencies	A	430	152	0.24	0.63	0.95 (0.76–1.18)	84	0.79	0.37	1.13 (0.86–1.49)	142	2.91	0.09	0.82 (0.65–1.03)	96	0.01	0.91	1.02 (0.78–1.32)
		C	1058	354				234				286				240			
Q126X	Genotype frequencies	CT	6	1		0.69		1		1		1		1		0		0.60	
		CC	738	252				158				212				168			
	Allele frequencies	T	6	1		0.69	2.05 (0.25–17.02)	1		1	1.28 (0.15–10.70)	1		1	1.73 (0.21–14.40)	0		0.60	
		C	1482	505				317				427				336			

OR = 1.11, 95% *CI* 0.74–1.65 by allele; severe PE without HUA: X^2 = 0.29, *P* = 0.86 by genotype; X^2 = 0.23, *P* = 0.63, *OR* = 1.06, 95% *CI* 0.85–1.32 by allele). The same case displayed in Q126X between mild/severe PE with HUA, mild/severe PE without HUA and controls (mild PE with HUA: *P* = 0.39 by genotype; *P* = 0.39, *OR* = 0.43, 95% *CI* 0.05–3.63 by allele; serve PE with HUA: *P* = 0.43 by genotype; *P* = 0.43, *OR* = 3.32, 95% *CI* 0.40–27.66 by allele; mild PE without HUA: *P* = 1 by genotype; *P* = 1 by allele; severe PE without HUA: *P* = 0.69 by genotype; *P* = 0.69, *OR* = 2.10, 95% *CI* 0.25–17.50 by allele).

Table 4 displayed no significant difference between early-onset/late-onset PE with HUA, early-onset/late-onset PE without HUA and controls in Q141K (early-onset with HUA: X^2 = 0.33, *P* = 0.85 by genotype; X^2 = 0.24, *P* = 0.63, *OR* = 0.95, 95% *CI* 0.76–1.18 by allele; late-onset PE with HUA: X^2 = 5.34, *P* = 0.07 by genotype; X^2 = 2.91, *P* = 0.09, *OR* = 0.82, 95% *CI* 0.65–1.03 by allele; early-onset PE without HUA: X^2 = 1.14, *P* = 0.56 by genotype; X^2 = 0.79, *P* = 0.37, *OR* = 1.13, 95% *CI* 0.86–1.49 by allele; late-onset PE without HUA: X^2 = 0.12, *P* = 0.94 by genotype; X^2 = 0.01, *P* = 0.91, *OR* = 1.02, 95% *CI* 0.78–1.32 by allele). There was also no statistical difference in Q126X between early-onset/late-onset PE with HUA, early-onset/late-onset PE without HUA and controls (early-onset with HUA: *P* = 0.69 by genotype; *P* = 0.69, *OR* = 2.05, 95% *CI* 0.25–17.02 by allele; late-onset PE with HUA: *P* = 1 by genotype; *P* = 1, *OR* = 1.73, 95% *CI* 0.21–14.40 by allele; early-onset PE without HUA: *P* = 1 by genotype; *P* = 1, *OR* = 1.28, 95% *CI* 0.15–10.70 by allele; late-onset PE without HUA: *P* = 0.60 by genotype, *P* = 0.60 by allele).

4. Discussion

As an unique and multifactorial disorder of women pregnancy, PE is a strong genetic predisposition in the development, and no less than 50 candidate genes including *F5* (Factor V Leiden), *AGT* (Angiotensinogen), *EDN1* (Endothelin 1), *IL1RN* (Interleukin 1 receptor antagonist), *EPHX1* (Microsomal epoxide hydrolase) and *APOL1* (apolipoprotein L-1) have been related to the likely genetic risk factors for PE [23,24]. Inadequate uteroplacental circulation, placental dysfunction, oxidative stress, the instability of angiogenic and anti-angiogenic factors may influence a systemic endothelial dysfunction, which may play crucial roles in the pathogenesis of PE [5]. HUA in preeclamptic women usually preceding hypertension and proteinuria not only is a reminder of tissue injury, renal dysfunction and oxidative stress but also contributes directly to the pathogenesis of PE [1,4,5]. With the development of PE, a combination of several factors, such as the proinflammatory state, the endothelial lesion and reduction of the glomerular filtration, decreases UA excretion and increases HUA. Moreover, the fetuses exposed to hypoxia could increase the production of purine metabolites in serum to aggravate HUA due to the decrease of the placental perfusion [5]. Therefore, these two diseases not only facilitate the occurrence but also bring about the consequence for each other.

The balance of UA production and excretion decides the level of SUA, and underexcretion is the primary reason of HUA by the kidney (70%) and the gut (30%) [6,10]. A serious of secretory and reabsorptive transporters expressed on the basolateral and apical membrane could act as urate-lowering agents [25]. GWAS focused on renal urate-transport system encoding proteins including *GLUT-9*, *URAT1*, *SL* X^2*2A6, SL* X^2*2A8*, *SL* X^2*2A11* and *SL* X^2*2A13* (solute carrier family 22 member 6, member 8, member 11, and member 13), *MRP4* (multi drug resistance-associated protein 4), *SLC5A8, SLC5A12* (sodium coupled monocarboxylate transporter 1, 2), *PDZK1* and *ABCG2* [9], which involve in the balance of UA. Among them, *ABCG2* and *GLUT-9* have a very strong effect on the serum urate concentrations within the 28 genetic loci associated with the risk of HUA in the sample sets of New Zealand European and Polynesian people [26]. Kottgen et al. identified that *ABCG2* contributed the largest increases in SUA (0.217 mg/dl) and

resulted in the highest OR for gout risk (1.73) in a GWAS which researched a total of 28 associated with SUA genome-wide significant loci in a population of more than 140,000 principally European individuals [27]. They also strongly argued that the dysfunction of ABCG2 gave rise to extra-renal underexcretion, which may result in a compensatory increase of the renal urate output suggesting a critical importance of role in HUA and gout risk in a series of elegant researches [6,8,10,13,14,28]. Jiska et al. indicated that ABCG2 significantly expressed in the placenta could protect fetus from xenobiotics and some cellular accumulation of cytotoxic compounds, while its expression was reduced in pregnancies of PE complicated by HELLP syndrome [29].

The membrane-associated protein encoded by *ABCG2* is part of the superfamily of ATP-binding cassette (ABC) transporters including seven distinct subfamilies, ABC1, MRP, MDR/TAP, OABP, ALD, GCN20 and White, and ABCG2 is one of the White subfamily. As a well-known high-capacity urate exporter for urate excretion and reabsorption, the dysfunction of ABCG2 reduced UA efflux highly dependent on the intracellular concentration of the urate exporter [10]. As two important functional variants, Q141K and Q126X may affect the ABCG2 nucleotide-binding domain and influence the expression levels of ABCG2, which may contribute risk to HUA and gout [8,14]. Q141K variant occurs in the most conserved region ABC proteins where a residue of nucleotide binding domain was critical to interchanges with the intracellular loops of the protein transmembrane portion [13]. The Q141K polymorphism changing glutamine to lysine substitution at position 141 may result in approximately 50% reduction of the expression and function of transport urate while Q126X variant coding glutamine to termination codon substitution at position 126 may result in entire dysfunction of the transport urate. Therefore, the dysfunctional genotypic combinations of Q141K and Q126X are most significant reason to for HUA [16,30]. As there's no definite effective approach to prevent PE currently and the only effective treatment is delivery, it is necessary to carry out early intervention through like genetic testing to enhance appropriate application of antenatal care, treatment and management and reduce the occurrence of adverse consequences. As Q141K and Q126X in *ABCG2* play the important roles in HUA which is of great importance to the development of PE, we designed this research to explore the relationship between these polymorphisms and PE in Chinese women population.

As a breast cancer resistance protein and a xenobiotic transporter, ABCG2 also acts a major role in multi-drug resistance. Some research showed that placental expression of ABCG2 decreases with advancing gestation [31]. In addition, Afrouzian et al. believed that preterm placentas with inflammation and PE had an increase expression of ABCG2 [32]. Previous reports have been indicated that ABCG2 dysfunction was associated with serum uric acid concentration and gout in white, black individuals as well as yellow individuals such as Japanese, Koreans and Chinese [6,16,28]. Wang et al. showed women with PE had a higher - prevalence of developing gout in their following years [33], suggesting the pathogenesis of Gout and PE have commonality and overlap at the genetic level.

However, we found no statistically significant difference between Q141K and Q126X in *ABCG2* and PE in the genotype including dominant and recessive model and allele frequencies between PE and the normal pregnant women in our present study, and also no difference in genotypic and allelic distribution of Q141K and Q126X between PE with HUA, PE without HUA and controls. When divided PE with/without HUA into mild/severe PE with/without HUA and early-onset/late-onset PE with/without HUA, we observed still no significant difference between each of these groups and the normal controls. Therefore, the polymorphisms of ABCG2 Q141K and Q126X may not be associated with PE in Chinese Han women. However, we should further seek for other variants related to SUA in *ABCG2* or in other genes with a larger scale to explore their relationship to achieve the goal of early diagnosis and prevention in the future study.

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Declaration of Competing Interest

We declare that we have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.06.006.

References

[1] O.P. Khaliq, T. Konoshita, J. Moodley, T. Naicker, The role of uric acid in pre-eclampsia: is uric acid a causative factor or a sign of preeclampsia? Curr. Hypertens. Rep. 20 (9) (2018) 80.
[2] A. Trevino-Becerra, Uric acid: the unknown uremic toxin, Contrib. Nephrol. 192 (2018) 25–33.
[3] S. Masoura, K. Makedou, T. Theodoridis, A. Kourtis, L. Zepiridis, A. Athanasiadis, The involvement of uric acid in the pathogenesis of preeclampsia, Curr. Hypertension Rev. 11 (2) (2015) 110–115.
[4] M.J. Schmella, R.G. Clifton, A.D. Althouse, J.M. Roberts, Uric acid determination in gestational hypertension: is it as effective a delineator of risk as proteinuria in high-risk women? Reproductive Sci. (Thousand Oaks, Calif). 22 (10) (2015) 1212–1219.
[5] A.A. Moreno Santillan, J.C. Briones Garduno, M.A. Diaz de Leon Ponce, Uric acid in pregnancy: new concepts, Contrib. Nephrol. 192 (2018) 110–115.
[6] C.N. Son, S.Y. Bang, ABCG2 polymorphism is associated with hyperuricemia in a study of a community-based Korean cohort. 2017;32(9):1451-9.
[7] F. Yan, P. Sun, H. Zhao, C. Zhao, N. Zhang, Y. Dai, Genetic association and functional analysis of rs7903456 in FAM35A gene and hyperuricemia: a population based study, Sci. Rep. 8 (1) (2018) 9579.
[8] M.C. Cleophas, L.A. Joosten, L.K. Stamp, N. Dalbeth, O.M. Woodward, T.R. Merriman, ABCG2 polymorphisms in gout: insights into disease susceptibility and treatment approaches, Pharmacogenomics Pers. Med. 10 (2017) 129–142.
[9] A.M. Reginato, D.B. Mount, I. Yang, H.K. Choi, The genetics of hyperuricaemia and gout, Nat. Rev. Rheumatol. 8 (10) (2012) 610–621.
[10] O.M. Woodward, ABCG2: the molecular mechanisms of urate secretion and gout, Am. J. Physiol. Renal Physiol. 309 (6) (2015) F485–F488.
[11] W. Li, D. Zhang, F. Du, X. Xing, Y. Wu, D. Xiao, et al., ABCB1 3435TT and ABCG2 421CC genotypes were significantly associated with longer progression-free survival in Chinese breast cancer patients, Oncotarget 8 (67) (2017) 111041–111052.
[12] M. Huls, C.D. Brown, A.S. Windass, R. Sayer, J.J. van den Heuvel, S. Heemskerk, et al., The breast cancer resistance protein transporter ABCG2 is expressed in the human kidney proximal tubule apical membrane, Kidney Int. 73 (2) (2008) 220–225.
[13] B. Stiburkova, K. Pavelcova, J. Zavada, L. Petru, P. Simek, P. Cepek, et al., Functional non-synonymous variants of ABCG2 and gout risk, Rheumatology (Oxford, England). 56 (11) (2017) 1982–1992.
[14] K. Fujita, K. Ichida, ABCG2 as a therapeutic target candidate for gout, 2018, 22(2), 123–129.
[15] H. Matsuo, K. Yamamoto, H. Nakaoka, A. Nakayama, M. Sakiyama, T. Chiba, et al., Genome-wide association study of clinically defined gout identifies multiple risk loci and its association with clinical subtypes, Ann. Rheum. Dis. 75 (4) (2016) 652–659.
[16] M. Nakamura, K. Fujita, Y. Toyoda, T. Takada, H. Hasegawa, K. Ichida, Investigation of the transport of xanthine dehydrogenase inhibitors by the urate transporter ABCG2, Drug Metab. Pharmacokinet. 33 (1) (2018) 77–81.
[17] A. Meeme, G.A. Buga, M. Mammen, A. Namugowa, Endothelial dysfunction and arterial stiffness in pre-eclampsia demonstrated by the EndoPAT method, Cardiovasc. J. Africa 28 (1) (2017) 23–29.
[18] C. Borghi, A. Tykarski, K. Widecka, K.J. Filipiak, J. Domienik-Karlowicz, K. Kostka-Jeziorny, et al., Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk, Cardiol. J. 25 (5) (2018) 545–563.
[19] R.W. Powers, L.M. Bodnar, R.B. Ness, K.M. Cooper, M.J. Gallaher, M.P. Frank, et al., Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricemia at delivery, Am. J. Obstet. Gynecol. 194 (1) (2006) 160.
[20] L.A. Magee, A. Pels, M. Helewa, E. Rey, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary, J. Obstetrics Gynaecol. Canada: JOGC = Journal d'obstetrique et gynecologie du Canada: JOGC 36 (7) (2014) 575–576.
[21] J. Wang, Y. Lin, F. Lv, H. Hou, K. Chu, B. Jiang, et al., Effects of Klotho

polymorphisms on Preeclampsia risk in a case-control study, Pregnancy Hypertension 13 (2018) 95–99.
[22] I. Alvarez-Fernandez, B. Prieto, V. Rodriguez, Y. Ruano, A.I. Escudero, F.V. Alvarez, New biomarkers in diagnosis of early onset preeclampsia and imminent delivery prognosis, Clin. Chem. Lab. Med. 52 (8) (2014) 1159–1168.
[23] K.J. Reidy, R.C. Hjorten, C.L. Simpson, A.Z. Rosenberg, S.D. Rosenblum, C.P. Kovesdy, et al., Fetal-not maternal-APOL1 genotype associated with risk for preeclampsia in those with African ancestry, Am. J. Hum. Genet. 103 (3) (2018) 367–376.
[24] S. Chappell, L. Morgan, Searching for genetic clues to the causes of pre-eclampsia, Clin. Sci. (London, England: 1979) 110 (4) (2006) 443–458.
[25] M. Chen, X. Lu, C. Lu, N. Shen, Y. Jiang, M. Chen, et al., Soluble uric acid increases PDZK1 and ABCG2 expression in human intestinal cell lines via the TLR4-NLRP3 inflammasome and PI3K/Akt signaling pathway, Arthritis Res. Therapy 20 (1) (2018) 20.
[26] A.J. Phipps-Green, M.E. Merriman, R. Topless, S. Altaf, G.W. Montgomery, C. Franklin, et al., Twenty-eight loci that influence serum urate levels: analysis of association with gout, Ann. Rheum. Dis. 75 (1) (2016) 124–130.
[27] A. Kottgen, E. Albrecht, A. Teumer, V. Vitart, J. Krumsiek, C. Hundertmark, et al., Genome-wide association analyses identify 18 new loci associated with serum urate concentrations, Nat. Genet. 45 (2) (2013) 145–154.
[28] B. Wang, Z. Miao, S. Liu, J. Wang, S. Zhou, L. Han, et al., Genetic analysis of ABCG2 gene C421A polymorphism with gout disease in Chinese Han male population, Hum. Genet. 127 (2) (2010) 245–246.
[29] J. Jebbink, G. Veenboer, S. Boussata, R. Keijser, A.E. Kremer, R.O. Elferink, et al., Total bile acids in the maternal and fetal compartment in relation to placental ABCG2 expression in preeclamptic pregnancies complicated by HELLP syndrome, Biochim. Biophys. Acta 1852 (1) (2015) 131–136.
[30] T. Higashino, T. Takada, H. Nakaoka, Y. Toyoda, B. Stiburkova, H. Miyata, et al., Multiple common and rare variants of ABCG2 cause gout, RMD Open 3 (2) (2017) e000464.
[31] P.J. Williams, H.D. Mistry, L. Morgan, Folate transporter expression decreases in the human placenta throughout pregnancy and in pre-eclampsia, Pregnancy Hypertension 2 (2) (2012) 123–131.
[32] M. Afrouzian, R. Al-Lahham, S. Patrikeeva, M. Xu, V. Fokina, W.G. Fischer, et al., Role of the efflux transporters BCRP and MRP1 in human placental bio-disposition of pravastatin, Biochem. Pharmacol. 156 (2018) 467–478.
[33] I.K. Wang, J.H. Chen, C.H. Muo, C.Y. Chou, Y.L. Liu, S.Y. Lin, et al., Subsequent risk of gout for women with hypertensive disorders in pregnancy: a retrospective cohort study, J. Hypertens. 34 (5) (2016) 914–919.